Weaning Infants with Respiratory Syncytial Virus from Mechanical Ventilation through a Fuzzy-Logic Controller

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We have previously developed a fuzzy logic controller for weaning adults with chronic obstructive pulmonary disease using pressure support ventilation (PSV). We used the core of our fuzzy logic-based weaning platform and further developed parametrizable components for weaning newborns of differing body size and disease-state. The controller was validated on neonates recovering from congenital heart disease (CHD) while receiving synchronous intermittent mandatory ventilation (SIMV). We wished to compare the efficacy of this controller versus the bedside weaning protocol in children with respiratory syncytial virus pneumonitis/bronchiolitis (RSV) in the pediatric intensive care unit (PICU). The fuzzy controller evaluated the "current" and "trend" weaning status of the newborn, to quantitatively determine the change in the SIMV integrated ventilatory setting. For the "current" status, it used heart rate (HR), respiratory rate (RR), tidal volume (V_T) and oxygen saturation (SaO_2), while for the "trend" status, the differences of $\Delta RR/\Delta t$, $\Delta HR/\Delta t$, and $\Delta SaO_2/\Delta t$, recorded between two subsequent time points, were utilized. The enumerated vital signs were fuzzified and then probability levels of occurrence were assigned. Individualized "golden" goals for SaO_2 were set for each newborn. We retrospectively assessed the charts of 19 newborns, 113±128 days old, 5,546±2,321 gr body weight, weaning for 99±46 days, at 2-hour intervals. The SIMV levels proposed by the fuzzy controller were matched to those levels actually applied. In 60% of the time both values coincided. For the remaining 40%, the controller was more aggressive suggesting lower values of SIMV than the applied ones. The Area under the SIMV curves over time was 1,969±1,044 for the applied vs 1,886±978 for the suggested levels, respectively. The fuzzy controller, adjusted for body size and disease-pattern, can approximate the actual weaning course of newborns with RSV.

INTRODUCTION

Mechanical Ventilation & Weaning: Mechanical ventilation has the goal of stabilizing the patient's condition by restoring adequate gas exchange, unloading the work of the respiratory muscles, and preventing respiratory complications, until the cause of the respiratory insufficiency can be controlled and possibly cured. Weaning from mechanical ventilation may be achieved by the gradual reduction of ventilatory support until normal spontaneous breathing can be fully resumed. During the weaning process, the intensivist defines the mechanical parameters of ventilation (i.e. flow, volume) in an experiential manner, based upon the measurement of some quantifiable physiological parameters (surrogate markers). This is an empiric method hindered by the lack of endpoints[1] to ventilation, weaning and extubation[2], with the ventilatory settings frequently being altered only twice daily. This slow and infrequent reassessment of clinical status may result in prolongation of assisted ventilation, delayed extubation, increased risk of nosocomial infections, all resulting in prolonged hospitalization[3, 4].

The automated control of mechanical ventilation has been investigated, mostly in terms of weaning and the appropriateness of the ventilatory support provided to a patient[5-7]. Automation/computerization of this process should depend upon how well the functions, traditionally performed by a physician, can be implemented using computers to control medical devices. Traditionally, weaning modes of ventilation (in children) have been: a) synchronized intermittent mandatory ventilation and b) pressure support ventilation. However, due to the complexity of the clinical problem, continuous monitoring of the patient's condition and frequent adjustments of the ventilatory support need to be made, to avoid excessive work of breathing, and advance the patient towards extubation. The risk, however, is that incompatible mechanical ventilation parameters may lead to patient-ventilator asynchrony (patient fighting the ventilator) with ensuing difficulties in gas exchange (i.e. hypoxemia, hypercapnia), increased intrathoracic pressure, increased impedance to respiratory muscle function, and compromise of cardiovascular function[3]. It is with these limitations that complex computational interpretation (using a computer-controlled system) may ensure both uniformity of monitoring, and proportional application of predetermined responses to aberrations in ventilatory function[8-12].

Previously, we have developed a fuzzy logic-based controller of breathing for weaning intubated adults under PSV, with chronic obstructive pulmonary disease in the ICU[10, 13]. We then extended the core

concepts of this fuzzy controller in infants. We used adaptive fuzzification rules to address the diversified weaning strategies seen in newborns. We tested this controller in infants weaning post-operatively, following surgical procedures for cyanotic congenital heart disease[14] (Transposition of the Great Vessels, Tetralogy of Fallot). We wished to test the efficacy of the fuzzy controller in infants with intrinsic lung disease, Respiratory Syncytial Virus pneumonitis/ bronchiolitis.

RSV Weaning: A number of unique physiologic and pathophysiologic features exist in the infant ventilated for respiratory failure, in the setting of RSV bronchiolitis, the implication being that there are several distinctions in weaning this population from mechanical ventilation as compared to those infants with otherwise healthy lungs, intubated for a non-respiratory indication.

The two primary pathophysiologic features which characterize this process are small airway edema/ inflammation and airway hyperreactivity. The consequence of both of these is a marked increase in airway resistance, moreso in expiration but also to a degree during inspiration. Additional to the expected gas-trapping and hyperinflation that is typically seen, there is a marked perturbation of normal respiratory mechanics and a predictable and often dramatic increase in work of breathing. It is this increased work of breathing that leads to hypercarbia and respiratory muscle fatigue, with impairment of minute ventilation and rapid onset of respiratory failure. Despite this proclivity for hypercarbic respiratory failure, the primary gas exchange abnormality observed in this setting is in fact hypoxemia, the result of impaired ventilation/perfusion matching and an increase in physiologic dead space. As such there exist a number of alterations in respiratory mechanics and gas exchange in the infant with viral small airway disease that complicate the process of weaning from mechanical ventilation. While it is true that much of the aim of mechanical ventilatory support in this setting is to overcome this exaggerated work of breathing and allow for resolution of the primary pathophysiologic process, many of these physiologic perturbations persist into convalescence and have significant implications in the weaning process. It is these considerations that distinguish the infants with RSV from those weaned from mechanical ventilation for a non-respiratory indication, and have necessitated several modifications and adaptations to the aforementioned fuzzy logic controller.

BACKGROUND

The concepts of: a) surrogate markers and b) mathematical modeling, play a key role in the computer driven ventilation control in an attempt to define, dynamically, the ability and capacity of the respiratory system to attain physiologic homeodynamic equilibrium in response to metabolic demands.

Surrogate markers like: respiratory frequency (RR); tidal volume (V_T); minute ventilation ($\dot{V}_E$); gas diffusion PaO_2, $PaCO_2$, $P(A\text{-}a)O_2$ and pH; muscle strength PI_{max}; oxygen saturation (SaO_2) and heart rate (HR); reflect major components of the respiratory system including ventilatory drive, ventilatory reserve, and efficacy of gas exchange. It has previously been demonstrated, in adults, that the proper interpretation of these markers may both predict the pattern and timing of changes in mechanical ventilation, as well as suggest the appropriate progression of weaning to independent ventilation[15].

Nevertheless, so far, there is no single established measurable variable or marker that can predict the progression of a mechanically ventilated patient towards extubation. Moreover, the existing surrogate markers provide multiple and complex patterns of results that cannot be easily assimilated nor analyzed quickly by the physician because of the complexity and rapidity of fluctuations. Indeed, more precise predictive markers that integrate much of the information available could be developed if the appropriate analytical tools were available. For these reasons, computers may facilitate predictive modeling-based tools, which in turn, sequentially, may assist these basic limitations in patient management and ultimately optimize medical decision-making during the active weaning process. Ultimately, successful modeling of the respiratory system should consider all the interactions seen between the ventilated subject - ventilator - drug - disease process.

To this end, the evaluation of an intubated mechanically ventilated patient, at any specific time point, requires not only the consideration of the current state of the individual, but also the overall trend in condition (defined by previous clinical, treatment, respiratory, oximetry and laboratory history), and the variability of the surrogate markers. Artificial intelligence methods (with or without fuzzy logic techniques) more closely represent subjective human decision making processes i.e. a variety of factors of relative importance are weighed against a

background of experience, thus mimicking medical decision making process[16]. A new area for this modelling technique, however, is the utility and applicability of fuzzy logic in decision making for strategies of mechanical ventilation[10, 13]. The currently existing algorithms for the control of mechanical ventilation are linear, and inadequately describe the complexities of the dynamic phenomenon of breathing. This might be accentuated by the fact that the efficacy of gas exchange is dependent on numerous factors, the quantification of which may be meaningful within the concept of data sets rather than discrete numbers. Artificial intelligence with fuzzy logic depends upon this concept such that linguistic characterisations can be used to quantify the variables. *Fuzzification* is the process enabling the segmentation of the allowable range into different categories for each variable, followed by the assignment of a linguistic characterization which represents the conceptual response to the magnitude of the variable. Once all the relevant variables (surrogates) are fuzzified, all their possible combinations and correlations with the end point are defined through the *fuzzy associative matrices*. For example, a *satisfactory* level of SaO_2, V_T and RR would indicate a normal breathing pattern.

MATERIALS AND METHODS

Fuzzy Controller: We postulate that the complete and accurate evaluation of an intubated and mechanically ventilated infant requires the consideration of both the CURRENT STATUS (RESPONSE) of the patient (mechanical respiratory support), as well as the TREND RESPONSE (suggested by the overall status over time) of the patient. This can be quantified by the past clinical, therapeutic, respiratory, saturation and laboratory history. Moreover, we hypothesize that the proper evaluation of vital signs - determining the magnitude of mechanical ventilatory parameters - can be addressed through linguistic characterizations that

RR	V_T	HR	SaO_2	CURRENT RESPONSE
Low(20,20,25,30)	A=0.50*V_{TGoal}	A=0.65*HR_{Goal}	A=0.88*SaO_2	Immediate
Acceptable(25,30,35,40)	B=0.75*V_{TGoal}	B=0.8*HR_{Goal}	B=0.92*SaO_2	Respond
Moderately	C=1.25*V_{TGoal}	C=0.9*HR_{Goal}	C=0.96*SaO_2	Acceptable
High(35,40,40,50)	D=1.50*V_{TGoal}	D=1.1*HR_{Goal}	D=1.04*SaO_2	Review
High(40,50,100,100)	Low(A,A,A,B)	E=1.2*HR_{Goal}	E=1.08*SaO_2	
	Acceptable(A,B,C,D)	F=1.35*HR_{Goal}	F=1.2*SaO_2	
	High(C,D,D,D)	Low(A,A,B,C)	Low(A,A,A,B)	
		Acceptable(B,C,D,E)	Moderately	
		High(D,E,F,F)	Low(A,B,B,C)	
			Goal(B,C,D,E)	
			High(D,E,F,F)	

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$\Delta RR/\Delta t$	$\Delta HR/\Delta t$	$\Delta SaO_2/\Delta t$	TREND RESPONSE
Panic Low(-20,-20,-10,0)	Panic Low (-40,-40,-20,-10)	A=-0.08*SaO_{2Goal}	Increase
Acceptable(-10,0,0,10)	Significantly	B=-0.04*SaO_{2Goal}	Respond
High(0,10,10,20)	Worse(-20,-10,-10,0)	C=0	Accept
PanicHigh(10,20,40,40)	Goal(-10,0,0,10)	D=0.04*SaO_{2Goal}	Review
	Worrysome(0,10,10,20)	E=0.08*SaO_{2Goal}	
	PanicHigh(10,20,40,40)	Concern(A,A,B,C)	
		Goal(B,C,C,D)	
		Review(C,D,E,E)	

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CURRENT RESPONSE	TREND RESPONSE	% SIMV CHANGE

Table 1: Fuzzification and rule table for CURRENT and TREND responses

Subject #	*Gender*	*Age (days)*	*Weight (gr)*	*SaO_2 Goal*	*Weaning (hr)*
1	F	70	5,100	>95%	48
2	M	35	5,100	>95%	78
3	M	35	5,000	>95%	164
4	M	150	4,400	>95%	98
5	F	60	4,560	>95%	56
6	F	30	3,210	>95%	106
7	M	30	5,000	>95%	148
8	M	390	7,010	>95%	84
9	F	480	12,600	>95%	180
10	M	35	3,000	>97%	144
11	M	21	4,000	>96%	134
12	F	120	7,200	>95%	96
13	M	125	8,400	>98%	50
14	F	205	6,700	>93%	52
15	F	32	4,000	>94%	76
16	F	29	4,000	>94%	36
17	F	63	4,000	>95%	74
18	M	34	4,100	>94%	76
19	F	210	8,000	>96%	182

Table 2: Study population, age in days, weight in grams and length of weaning in days

quantify the variations within datasets rather than describing or using discrete levels. To implement the fuzzy controller, we selected easily assessable, non-invasive vital signs containing adequate information to describe a patient's response to mechanical ventilation. Therefore, the levels of HR, SaO_2, RR and V_T were used to indicate the CURRENT RESPONSE at each time step, while their trends ($\Delta HR/\Delta t$, $\Delta SaO_2/\Delta t$ and $\Delta RR/\Delta t$), computed over two consecutive time points, concluded about the TREND RESPONSE.

To further add complexity to the model, the issue of the variation in size of infants was addressed to allow the physician to determine individualized goals for adequate levels of HR and V_T. Moreover, the underlying disease process (RSV) may require individualization of the acceptable, SaO_2 and $\Delta SaO_2/\Delta t$. Therefore, we introduced the concept of dynamic area identifiers in the fuzzification process based upon the percentage deviation from the "ideal" goal. For instance if the targeted HR is 134 beats/min, then any measure within a ±10% range is ACCEPTABLE while any other level laying outside this range can only be LOW (undershooting) or HIGH (overshooting). Different percentage variations for each of the "goals" for V_T, SaO_2 and $\Delta SaO_2/\Delta t$, have also been identified. On the contrary, RR, $\Delta RR/\Delta t$ and $\Delta HR/\Delta t$, although bound to the infant, are insensitive to the different disease-states. Furthermore, because our study group was age-consistent i.e. less than 1.5 years of age, the fuzzification of these variables was conceptualized through constant area identifiers.

Static and dynamic fuzzification is demonstrated in Table 1. Also, following the fuzzification of HR, V_T, SaO_2 and RR, proper linguistic quantifiable characterizations - that is 3, 3, 4 and 4, respectively - are assigned to each one of these variables. The

incurred 144 (= 3 x 3 x 4 x 4) combinations corresponding to the HR, V_T, SaO_2 and RR levels respectively, are assigned to the linguistic outcomes of "IMMEDIATE", "RESPOND", "ACCEPTABLE" and "REVIEW". We postulate that these outcomes adequately address the "CURRENT RESPONSE" of the intensivist as a feedback to the patient-ventilator interaction. The concept is similar for the "TREND RESPONSE" assessing the over time response of the patient to assisted ventilation. Thus, the levels of $\Delta HR/\Delta t$, $\Delta SaO_2/\Delta t$ and $\Delta RR/\Delta t$ were segmented into 5, 3 and 4 datasets, respectively, with an equal number of linguistic characterizations assigned to them. The 60 (= 5 x 3 x 4) possible linguistic combinations generated, were then assigned to one of the "INCREASE", "RESPOND", "ACCEPT" and "REVIEW" suggestions with reference to the ventilator's settings. The percentage that the SIMV level would be altered (with reference to the past setting), was indicated by the 16 (= 4 x 4) possible actions determined to address the CURRENT and TREND RESPONSES. To each one of these combinations 4 possible interventions were assigned: "INCREASE A LOT", "INCREASE", "REVIEW" and "DECREASE" the SIMV level. De-fuzzification of these characterizations and quantitative translation into a specific percentage of change was performed according to the CENTER OF GRAVITY of all the events and their corresponding probability of occurrence as defined through the previous steps.

Study Population & Design: Studies were performed on 19 infants in total (9 Male, 10 Female, Range: age 21-480 days, body weight 3,000-12,600 gr, weaning time 36-182 hr) who had severe RSV pneumonitis with prolonged ventilation. All infants were hospitalized in the PICU of the Montreal Children's Hospital of the McGill University Health Center (Table 2) and received ventilatory support from a Siemens 300 ventilator. The mode of ventilation used exclusively, was SIMV+PRVC targeting >8 mL/kg of V_T, with a $PaCO_2$ of <45 torr. The SaO_2 levels were individualized per patient. Although the total length of mechanical ventilatory support was longer (data not shown), weaning commenced with a ventilatory strategy of "permissive hypercapnea" ($PaCO_2 \leq 55$ torr). The onset of weaning - as initiated by the intensivist - was adopted as baseline for our observational study, while for the extubation all subjects had to be: a) responsive, b) clinically stable and improving, c) able to make some spontaneous breathing efforts without assisted ventilation and d) have a regular breathing pattern with $V_T \geq 4$ mL/kg, RR < 2 * (Normal RR for age) and MIP (or PI_{max}) ≥ -30 cmH_2O.

We retrospectively assessed the patients' charts to obtain HR, RR, V_T, SaO_2 and SIMV parameters at 2-hour intervals throughout the entire weaning phase. The trend levels of $\Delta HR/\Delta t$, $\Delta SaO_2/\Delta t$ and $\Delta RR/\Delta t$ were computed as the difference of two consecutively acquired (over time) data points of the corresponding signs. RR and V_T had been initially acquired from the Siemens ventilator, while HR and SaO_2 had been collected through a Nellcor N-200 pulse oximeter. We then used our fuzzy controller to arrive at suggestions about the CURRENT RESPONSE as well as the TREND RESPONSE, referring to the modification of the SIMV settings by the intensivist due to the patient-ventilator interactions.

Subject #	*AUC SIMV Applied*	*AUC SIMV Suggested*	*P-Level*
1	1,084	1,038	<0.001
2	1,362	1,358	<0.001
3	4,216	3,942	<0.001
4	1,960	1,952	<0.001
5	1,332	1,266	<0.001
6	2,206	2,100	<0.001
7	3,778	3,672	<0.001
8	1,538	1,450	0.003
9	3,126	2,936	<0.001
10	2,106	2,098	<0.001
11	3,206	2,989	<0.001
12	1,448	1,352	<0.001
13	1,128	1,100	0.116
14	738	708	0.0012
15	1,180	1,164	<0.001
16	541	512	<0.001
17	1,688	1,676	0.558
18	1,666	1,630	<0.001
19	3,110	2,897	<0.001

Table 3: SIMV levels applied vs suggested; P-levels and Area under the SIMV Curves over time for each subject

Statistics: We wished to explore whether the SIMV level applied versus the one suggested in every subject separately was expressed by different distributions. We thus used the Wald-Wolfowitz non-parametric test, with Siegel's adjusted p-value for sample size correction, to address our hypothesis. The Area Under the SIMV Curve (AUC) was computed for both levels (applied & suggested), in each subject separately, as the integral (trapezoidal rule) of the SIMV level over the time length that this was in effect.

RESULTS

We compared the SIMV suggestions of the fuzzy controller with the SIMV levels actually applied as per the medical charts. There was a statistical significant difference ($P<0.05$) between the distributions of the two SIMV levels (applied vs suggested) in most of the subjects (Wald-Wolfowitz with Siegel's adjusted p-value). The AUC of the SIMV distributions, indicated that the fuzzy controller suggestions had a tendency towards lower levels of ventilation in all subjects(Table 3).

CONCLUSIONS

We assessed the respiratory, oximetry and cardiac profiles of intubated infants with complications

originated from respiratory syncytial virus during synchronized intermittent mandatory ventilation support. We retrospectively followed pertinent vital signs acquired from bedside monitors over time, from the onset of weaning until extubation. The levels of these vital signs were filtered through our fuzzy logic-based controller, an alternative course of SIMV was generated and compared to the actually applied level of ventilation. Areas under the curve of time-prolonged level of ventilation were smaller when following the suggested course of this controller.

RSV, is the most common infection of the lower respiratory tract seen in neonates and children. It is estimated that up to 1% of infants worldwide, shortly after their birth, are diagnosed with RSV and thus hospitalized; of those, 10% may be intubated and mechanically ventilated. Ventilation may be prolonged up to an average of 4-7 days in non-premature infants and up to an average of 7-10 days in older children. These periods under mechanical ventilation may be extended (mean of 17 days) for the higher risk groups of premature neonates and infants with CHD. Furthermore, morbidity levels increase with prematurity, lung disease and co-existing heart disease. Therefore RSV is the major factor of acute respiratory exacerbations within the first 2 years of life, while up to 5 years of age, this disease accounts for the 60% of the incidences due to lower respiratory tract viruses[17, 18]. Literature review suggests that these rates are dependent on a variety of complications, thus the commonly seen 1.5% mortality rate for the RSV children, may be increased up to: 1) 3.5% if followed by cardiac or chronic pulmonary disease[18, 19], 2) 15% during cancer chemotherapy[19], 3) 40% in the case of human immunodeficiency virus[19] and 4) 73% in the case of congenital heart disease and pulmonary hypertension. Reports would also suggest[20] that environmental factors might have an effect on the onset of this disease, rising potential risks up to 69% with the 50% of all children having potentially experienced RSV complications at least twice within the first 2 years of life[17, 18]. It is obvious that any improvement in the ventilatory assessment of RSV weaning newborns would be scientifically meritorious.

The main question focuses on the prospective application of the fuzzy controller and the difficulties that may arise from the real-time implementation. Any potential mechanical difficulties may be accentuated by the health status of the patient, i.e. elevated elastance, airflow resistance (due to the pulmonary, chest wall and bronchial edema), secretions, ineffective pump function, etc. However, we do believe that proper alteration and fine tuning of the rule tables in the fuzzy controller may adequately address any changes that may potentially arise in the total workload.

We advocate that any controller of breathing should seriously consider any reactions initiated from the ventilated subject as a response to mechanical ventilation, therapeutic strategy, and drug administration, thus assimilating the course of weaning and success/failure to extubation. Such an approach, once successful, would not only shorten the weaning period but it would also minimize the risk of nosocomial infections and failure to extubation. In addition, these efforts would prevent substantial hospitalization costs and also be useful for standardization in large clinical trials (i.e. drug responses, ventilations modes, etc.). The entire concept may also be extended by addressing additional physiological responses through the use of complementary clinical information aiming at the improvement of the accuracy of the predictions. Along these lines, complementary numerical methods may have to be considered - i.e. neural networks, fuzzy neural networks and genetic algorithms - to address the multiplicity of the incurring combinations amongst the various (surrogate) markers and to identify the optimum time path for weaning.

Future directions in the evolution of this controller should address the impact of all the aforementioned factors prior to the ultimate test through a randomized clinical trial.

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Dr. Hatzakis - Assistant Professor, Department of Pediatrics, McGill University - is a FRSQ Chercheur Boursier Scholar (E-Mail: gchatz@po-box.mcgill.ca).

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